REMARKS

Claims 34-47, 51-55, 57- 70, and 72-88 are pending in the present application.

Applicants have amended Claims 47 to replace the phrase "wherein said measuring comprises measuring a reduction of viral load" with the phrase "wherein said measuring comprises measuring IgG levels." Applicants have added Claim 89. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. Support for the phrase "wherein said measuring comprises measuring IgG levels" can be found, for example, in Example 5, and elsewhere throughout the specification. Support for Claim 89 can be found, for example, in Example 5, and elsewhere throughout the specification.

On May 16, 2006, the undersigned, Examiner Li and Supervisor Campell held an interview regarding the Office Action mailed February 22, 2006. During the interview between the undersigned, Examiner Li and, Supervisor Campell, the restriction requirement, the claim objections, the enablement rejections under 35 U.S.C. § 112, first paragraph, the new matter rejections under 35 U.S.C. § 112, first paragraph, the provisional double patenting rejection, and the rejections under 35 U.S.C. § 103 raised in the Office Action were discussed. The undersigned and the Examiner reached the following agreements: (1) Claims 34-43, 46-49, 51-52, 57-67 and 72-80 are linking claims and will be examined. (2) Claims 81-84 and 85-88 limit dependent Claims 51 and 66, respectively and the objection to the claims would be removed. (3) The enablement rejection would be removed in view of Applicants' disclosure. (4) The new matter rejection would be removed in view of Applicants' disclosure, and Applicants' proposed amendment to Claim 47 to recite "wherein said measuring comprises measuring levels of IgG" or "wherein said measuring comprises measuring levels of IgM." (5). The double patenting rejection would be addressed by submitting a terminal disclaimer. (6) The § 103(a) rejection would be removed in view of Applicants' arguments.

Claims 34-47, 51-55, and 57-70, and 72-89 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed February 22, 2006. For the reasons set forth below, Applicants respectfully traverse.

Election/Restriction

The Examiner has noted that in Applicants' Amendment and Response to Restriction Requirement mailed December 13, 2005, Applicants elected invention I, A method for treating

HCV infection. The Examiner states that "Applicants are reminded to amend the claims to the scope of hepatitis C virus for reflecting *[sic]* examination on the merits." *Office Action* at 2. Applicants disagree, and maintain that the Examiner is required to examine the pending claims.

In the Restriction Requirement mailed on November 17, 2005, the Examiner noted that Claims 34-43, 46-49, 51-52, 57-67, and 72-80 "are link(s) *[sic]* invention groups I-II and III." Applicants responded to the Restriction Requirement by electing invention I without traverse. *See, Amendment and Response to Restriction Requirement* mailed Dec. 13, 2005. The pending claims are either linking claims (*i.e.*, Claims 34-43, 46-49, 51-52, 57-67, and 72-80) or relate specifically to the elected invention (*i.e.*, Claims 44, 45, 53, 54, 55, 68, 69, 70).

Pursuant to M.P.E.P. § 809,

> The linking claims must be examined with, and thus are considered part of, the invention elected. When all claims directed to the elected invention are allowable, should any linking claim be allowable, the restriction requirement between the linked invention must be withdrawn. Any claim(s) directed to the nonelected invention(s), previously withdrawn from consideration, which depends from or requires all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability.

The above demonstrates that, contrary to the Examiner's assertion, no amendment to the claims to limit the scope to HCV is necessary in light of the Restriction Requirement. Applicants respectfully request that the Examiner examine the linking claims and claims drawn to the elected invention as agreed during the interview on May 16, 2006.

Specification

The Examiner has objected to the specification under M.P.E.P. § 608.01 as containing an embedded hyperlink and/or other form of browser-executable code. To address the Examiner's objection, Applicants amended the specification to remove the embedded browser-executable code. Applicants respectfully request that the Examiner withdraw the objection to the specification.

Claim Objections

The Examiner has objected to Claims 81-84 and 85-88 under 37 C.F.R. § 1.75(c) as allegedly being in improper dependent form for failing to further limit the subject matter of Claims 51 and 66, respectively. Applicants respectfully disagree.

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Claims 51 and 66 recite "a viral antigen". Dependent Claims 81-84 and 85-88 further specify that "said viral antigen is a fragment of hepatitis C virus NS3 protein" that comprises various lengths of consecutive amino acids. As discussed during the interview of May 16, 2006, Claims 81-84 and 85-88 further limit Claims 51 and 66. Applicants respectfully request that the Examiner withdraw the Claim objections as agreed upon during the interview.

Rejections Under 35 U.S.C. § 112, first paragraph - Written Description/New Matter

Claim 47

The Examiner has rejected Claim 47 as allegedly failing to comply with the written description requirement. According to the Examiner, Claim 47 contains matter which was not described in the specification in such a way as to reasonably convey that Applicants had possession of the claimed invention at the time the application was filed.

Applicants have amended Claim 47 to replace the phrase "wherein said measuring step comprises measuring a reduction of viral load" with the phrase "wherein said measuring comprises measuring levels of IgG." Applicants maintain that the amendment to Claim 47 renders the Examiner's rejection moot. As stated above, support for the amendment to Claim 47 can be found, for example, in EXAMPLE 5. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claim 47 under 35 U.S.C. § 112, first paragraph.

Claims 34-45, 47, 51-55, 57-70, and 72-88

The Examiner has rejected Claims 34-45, 47, 51-55, 57-70, and 72-88 as allegedly failing to comply with the written description requirement. According to the Examiner, the rejected claims contain matter which was not described in the specification in such a way as to reasonably convey that Applicants had possession of the claimed invention at the time the application was filed. Specifically, the Examiner states that Claims 34, 46, 51 and 66 include the step of identifying a subject in need of an enhanced production of viral antigen-specific antibodies, increased titer of viral antigen-specific IgG antibodies, or an improvement in a T cell response. The Examiner maintains that the specification "does not have any description how each particular immune response is measured or access in a subject prior to be *[sic]* selected for using said composition comprising HCV viral antigen and ribavirin." *Office Action* at 4. Applicants respectfully disagree.

As agreed upon in the interview on May 16, 2006, the rejected claims are supported by the disclosure in the specification, which demonstrates that Applicants were in possession of the claimed invention at the time the application was filed, including the steps of 1) identifying subjects 2) providing an immunogenic composition and 3) measuring, as recited in the claims. *See*, Examiner's Interview Summary. Paragraph [0008], the specification states that embodiments relate to "methods of enhancing the immune response of an animal. ... An animal in need of a potent immune response to an antigen is identified and then is provided an amount of Ribavirin together with the antigen that is effective to enhance an immune response." Likewise, paragraph [0011] of the specification describes the identification of an animal in need of an enhanced immune response. At paragraph [0015], the specification defines an enhanced immune response as "significant increase in immune-mediated protection against the antigen, as [] demonstrated by an increase in the titer of antibody raised to the antigen and an increase in proliferative T-cell responses." In other words, the identification step recited in the rejected claims is fully supported by the specification, as demonstrated in paragraphs [0008], [0011] and [0015], and elsewhere throughout the specification.

The specification also includes working examples, *i.e.*, EXAMPLES 1-5, of how each of the steps recited in the claims is carried out. For example, paragraph [0025]. Paragraph [0025] describes the identification of subjects in need of an enhanced immune response. Specifically, paragraph [0025] describes assays "to determine the extent of adjuvant activity" (*e.g.*, the ability to enhance an immune response as defined in paragraph [0015]), in mice that were immunized with rNS3, thereby describing the "identification" of a subject in need of an enhanced immune response to a viral antigen. Paragraph [0025] also describes the step of providing to said subject an immunogenic composition comprising a viral antigen and ribavirin. Antibody production is measured as described in paragraph [0026] and enhanced antibody production and antibody titer are described in paragraph [0027]. In a similar token, EXAMPLE 3 describes the identification of a subject in need of an enhanced immune response (*e.g.*, T cell response) to a viral antigen in paragraph [0031]. Paragraph [0031] also describes providing the subject with a viral antigen and ribavirin, as well as measuring the T-cell response to said viral antigen. Measurement of IgG and IgM levels to a viral antigen are described in EXAMPLE 5, at paragraph [0044].

As demonstrated above, the disclosure in the instant specification demonstrates that Applicants were in possession of the claimed invention, including each and every step recited in the claims, *i.e.,* identifying, providing, and measuring. Applicants respectfully request that the Examiner withdraw the rejection, as agreed upon in the May 16, 2006 personal interview.

Rejection Under 35 U.S.C. § 112, first paragraph - Enablement

The Examiner has rejected Claims 34-47, 51-54, 57-69, and 72-80 as allegedly not being described in the specification in such a way as to enable one skilled in the art to make and use the full scope of the claimed invention. According to the Examiner, the specification is "enabling for inducing an enhanced immune response against a specific antigen comprising using a defined viral polypeptide antigen, does not reasonably provide enablement for producing an enhanced specific immune response against a viral antigen with any antigen encoded by an entire viral particle or even an entire HCV particle." *Office Action* at 4.

The Examiner correctly points out that

> State of art *[sic]* also teaches that HCV antigenic protein but not the whole HV genome is able to induce an immune response after administering into an animal. It is unpredictable whether you inject *[sic]* whole coding sequence of HCV genome into a subject will induce an enhanced immune response or produce a replicating or infectious hepatitis C viral RNA since transfecting a subgenomic HCV into a cell line can produce infectious HCV RNA in vitro as evidence by Lohman et al. (Science 1999, Vol. 285, pp. 110-113, see abstract) or an acute or persistent infection in vivo as evidenced by Forns et al. (PNAS 2000, Vol. 97, pp. 13318-13323, see abstract. *Office Action* at 5.

Further, the Examiner states that while the specification teaches that full length rNS3 and ribavirin enhance the immune response to NS3, the specification does not provide sufficient evidence or adequate guidance to support the scope of the claimed invention. According to the Examiner, "[t]he level of skill in the art to perform the full scope of invention *[sic]* should be at the PhD level or holding an advanced degree in virology and immunology for selecting a suitable 10 amino acids and test *[sic]* each of the selections for the ability of inducing an enhanced immune response." *Office Action* at 5. For the reasons set forth below, Applicants maintain that the rejected claims are enabled, as agreed upon during the May 16, 2006 interview.

As an initial matter, Applicants point out that the rejected claims recite "providing to said subject an *immunogenic composition* comprising a viral antigen and ribavirin." As such viral

antigens that fail to elicit an immune response are not encompassed by the claims. Applicants also wish to emphasize that, based on the understanding in the field, one of skill in the art would readily appreciate that the use of "an entire viral particle or even an entire HCV particle" would be inoperable in an immunogenic composition and, thus, one of skill in the art would not use an entire intact viral particle in an immunogenic composition. M.P.E.P. §2164.08(b) provides:

> The presence of inoperative embodiments within the scope of the claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *M.P.E.P. §2164.08(b).*

The specification includes considerable data demonstrating that ribavirin is an adjuvant when co-administered with an antigen. *See, e.g.,* Examples 1-5. The determination of whether a particular formulation of ribavirin and viral antigen enhances an immune response is straightforward and routine in the field. It does not require undue experimentation to make and use the claimed compositions. The determination of whether co-administration of a viral antigen and ribavirin enhances an immune response requires only the step of comparing the immune response produced when the formulation includes ribavirin to the immune response produced when the formulation does not contain ribavirin as described in the examples disclosed herein. It does not require undue experimentation to perform these tests. To the contrary, these tests are routinely conducted during the formulation of any immunogenic composition containing an adjuvant.

Further, as discussed during the interview on May 16, 2006, numerous viral antigens, including HCV viral antigens were known and publicly available to those skilled in the art at the time of filing of the instant application. By way of example, several viral antigens (including T cell epitopes) are described in U.S. Patent No. 6,419,931, filed February 16, 1994, and attached hereto as Exhibit 1. In other words, no experimentation is required to determine viral antigens.

In view of the above, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph for lack of enablement.

Double Patenting

The Examiner has provisionally rejected Claims 34-47, 51-55, 57-70 and 72-80 as being obvious over Claims 36-40, 42-55, and 57-65 of co-pending U.S. Patent application No.

10/817,591. Applicants submit herewith a Terminal Disclaimer, thereby addressing and overcoming the Examiner's provisional rejection of the claims. Applicants respectfully request that the Examiner withdraw the provisional double patenting rejection.

Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 34-47, 51-55, 57-70 and 72-88 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Hultgren et al. (*J. Gene. Virol.*, 1998, 79:2381-2391)("Hultgren") and Tam (U.S. Patent No. 5,767,097)("Tam"). According to the Examiner:

> Tam R. teaches a method for producing an enhanced immune response, preferentially*[sic]* the TH1 type immune response to a specific antigen by administering a composition comprising a viral component with a non-viral component of ribavirin*[sic]* into patient (Claims 1-9). Tam et al. does not teach to use *[sic]* HCV antigen for the *[sic]* co-administration. *Office Action* at 7.

The Examiner asserts that Hultgren et al. teach a method for inducing an enhanced Th1-type immune response by administering HBV and HCV antigens on the basis of daily administration of ribavirin. The Examiner argues:

> Hultgren et al. teach a method for inducing an enhanced TH-1 type cellular immune response, such as Th1 type of cytrokine secretion, such as IL2 or INFγ*[sic]* (Fig. 5) for HBV e Antigen and Th-1 type humoral immune response for both HBV e antigen (Fig. 4 and 5) and HCV NS3 (Fig. 4) by administering HBV e antigen, core antigen and HCV NS3 in combination of*[sic]* ribavirin at 0.75-1.5mg per day in mice (see Methods on pages 2382-2383). Hultgren et al. conclude that the co-administration of ribavirin with HCV antigen produces an enhanced Th-1 type humoral and cellular immune response against said specific hepatitis viral antigen. *Office Action* at 7.

Lastly, the Examiner argues that co-administration of the viral antigen and ribavirin, as recited in the rejected claims, is merely "a designed*[sic]* choice since the functions exhibited by the two drugs administrated*[sic]* either separately or simultaneously are same*[sic]*" and thus the claimed invention is obvious absent unexpected results. *Office Action* at 8. Applicants respectfully disagree. As discussed at length during the interview on May 16, 2006 and as agreed upon by the Examiner, the Examiner's supervisor, and the undersigned, the instant claims are not obvious in view of Hultgren et al. and Tam.

Hultgren et al. disclose that daily ribavirin therapy accompanied by an immunization with an antigen and Freund's adjuvant results in **a shift in IgG subclass distribution,** with the most marked increases in IgG2a and IgG2b, however, contrary to Applicants' results, Hultgren et al. reported **no difference in the total IgG levels between the treatment groups.** (See, Fig. 4 and p. 2386, ¶1). In other words, Hultgren et al. disclose immune modulation, not an enhanced immune response. The difference between immune modulation and an enhancement of an immune response was discussed during the personal interview on April 15, 2003 between the undersigned, the Examiner, and the Examiner's Supervisor during the prosecution of the parent of the instant application, issued U.S. Patent No. 6,680,059. This same point was also discussed in the personal interview on May 16, 2006 concerning the instant case. At both interviews, the Examiner, the Supervisor, and the undersigned agreed that Hultgen et al. did not obtain an enhanced immune response.

Applicants would like to emphasize that the term adjuvant, as it has been and is being used in the vaccine field, stems from the Latin word "adjuvare" which means to help. Thus, an adjuvant should help, not merely shift or modulate, the antigen in the vaccine to become more immunogenic. Applicants have discovered that when co-administered with viral antigens, ribavirin functions as an adjuvant, *i.e.*, it enhances the immune response to the antigen.

In contrast to the findings provided by Hultgren et al., Applicants' specification demonstrates that when antigen and ribavirin are co-administered, and enhanced immune response is obtained. *See, Specification,* Fig. 1, Fig. 2, and Table 1. For example, Figure 1 shows that 10μg of antigen co-administered with 1 mg of ribavirin generates nearly the same mean antibody titer against the antigen as an immunization with 100μg of antigen without co-administration of ribavirin. Figure 2 shows that wide ranges of ribavirin concentrations, when co-administered with antigen, produces an adjuvant effect. Table 1 shows that by adding ribavirin to a sub-optimal vaccine dose of a commercially available preparation, antigen-specific specific antibodies became detectable. In the absence of ribavirin, no detectable antibodies were observed with the sub-optimal vaccine dose. These data demonstrate the enhanced immune response obtained from co-administration of ribavirin and an antigen is significantly different and unexpected from the immune modulation obtained from daily ribavirin therapy combined with administration of antigen. *c.f.* Hultgren et al. Fig. 4 and p. 2386, ¶1.

As agreed upon during the May 16, 2006 interview, Hultgren et al. teach away from co-administration of ribavirin and an antigen to enhance an immune response to the antigen. The authors report, for example, that "[t]he highest dose of daily ribavirin completely prevented anti-HBe seroconversion whereas lower ribavirin doses reduced antibody titers (Fig. 4c)." *Id.* at p. 2387, ¶1. Hultgren et al. also report that "[w]e show that ribavirin treatment causes a transient drop in HCV-specific humoral responses during treatment of patients with chronic HCV infection." *Id.* at p. 2388-2389. Still further, the authors state that "[r]ecent studies have indeed shown that ribavirin is immune-suppressive *in vitro*" and that "similar effects may well be present *in vivo* during treatment of chronic viral hepatitis." *Id.* at p. 2389 ¶2. Lastly, the authors report that "[h]igh daily doses of ribavirin (>1mg/day) applied to HBeAg-Tg mice totally inhibited anti-HBe seroconversion, clearly showing the immune-suppressive effects of ribavirin *in vivo*." *Id.* at p. 2389 ¶5 (emphasis added).

As demonstrated above, there is no evidence, motivation, or suggestion in the Hultgren et al. reference that daily ribavirin therapy combined with an immunization with an antigen enhances an immune response to the antigen. To the contrary, upon reading Hultgren et al., one of skill in the art would be strongly dissuaded from co-administering ribavirin and an antigen for enhancing an immune response to the antigen given the data presented. The ability to enhance an immune response to an antigen by co-administering the antigen with ribavirin is significantly different than the findings above and unexpected -- it is the complete opposite result as that reported in Hultgren et al.

Tam (U.S. Patent No. 5,767,097A) was also discussed at great length at the personal interviews of April 15, 2003 in the parent application and the May 16, 2006 in the instant application, and was traversed. To recap that discussion, Applicants pointed out that Tam only describes conventional daily ribavirin therapy. Tam states:

> In a preferred embodiment, ribavirin is administered orally to a human patient in a dosage which achieves a blood serum level averaging 0.25-12.5μg/ml, and most preferably, approximately 2.5μg/ml. In a typical individuals[*sic*], this optimimum [*sic*] serum level, works out to be approximately 4.5 mg/kg/day of body weight which can be administered in doses from 200-1200 mg. Preferably the dosages are divided into a number of smaller doses which are then administered throughout the day.

> Since ribavirin has been on the market for several years, many dosage forms and routes of administration are known, and all appropriate dosage forms and routes of administration may be utilized. For example, in addition to oral administration, ribavirin may given intravenously, intramuscularly, intraperitoneally, topically, and the like, all of which are known. *(See Column 4, lines 25-41).*

Furthermore, in no place does Tam describe administration of ribavirin with an antigen. Claim 6 states:

> 6. A method of treating a patient having a disease which includes a viral component and a non-viral component, the non-viral component being characterized by reduced Th1 levels and increased Th2 levels in activated T-lymphocytes, comprising administering Ribavirin to the patient under a protocol sufficient to promote the Th1 response and suppress the Th2 response in a patient.

The claim simply recites the treatment of a patient with a viral disease ("having a disease which includes a viral component") by providing ribavirin. As discussed at length previously, in Tam, there is no evidence, indication, suggestion or motivation for administering any composition with an antigen much less a composition comprising an antigen and ribavirin. During both the April 15, 2003 and May 16, 2006 personal interviews, it was agreed upon by the Examiner and the undersigned that this is a mischaracterization of the teachings of Tam.

Furthermore, as in Hultgren et al., Tam teaches away from Applicant's claimed invention. Tam states:

> In addition, we have significantly advanced the prior research by demonstrating that ribavirin modulates the cytokine pattern of an immune response at least in part by promoting a Th1 response and suppressing a Th2 response. In hindsight, this discovery is not inconsistent with prior research. First, ribavirin is known to inhibit both functional humoral immune responses, (Peavy et al, 1981, J Immunol 126: 861-864, Powers et al, 1982, Antimicrob Agents Chemother 22: 108-114) and IgE-mediated modulation of mast cell secretion (Marquardt et al, 1987, J Pharmacol Exp Therapeutics 240: 145-149, (both Th2 lymphokine-mediated events). *(See Column 2, lines 65-67 and Column 3, lines 1-9).*

Again, the prior art emphasizes that ribavirin is an immune-suppressive agent, not an adjuvant. Based on the arguments above, it was determined at the personal interview of May 16, 2006 that the claims, which recite "providing an immunogenic composition comprising a viral antigen and ribavirin" are not unpatentably obvious over Hultgren et al. in view of Tam.

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To recap, Applicants respectfully submit that neither Hultgren et al. nor Tam teach co-administration of ribavirin and an antigen. Both references describe daily ribavirin therapy and the Examiner has misinterpreted Tam, specifically Claim 6, to describe administration of viral antigen. It is the patient that has a disease, which includes a viral component, not the composition being administered. Second, not only does the combination of Tam and Hultgren et al. not teach co-administration and, thus, cannot make the claimed invention prima facie obvious, but, as discussed above, daily ribavirin therapy combined with an immunization with an antigen produces a significantly different result than Applicants' claimed invention. It is unexpected that an enhanced immune response can be obtained by co-administering ribavirin and an antigen. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

The undersigned has made a good-faith effort to respond to the Office Action and to place the claims in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call Applicants' attorney, Eric S. Furman, Ph.D., at (619) 687-8643 (direct line) to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

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Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 22, 2006

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